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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/441,318	11/16/1999	PATRICIA L. CONKLIN	BTI-41	4166

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EXAMINER	
KUBELIK, ANNE R	
ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/441,318	CONKLIN ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *16 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22 and 24-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22 and 24-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *with the application* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The finality of the rejection of the last Office action is withdrawn in light of the new rejections below.

2. This application contains claims drawn to sequences referred to by GenBank Accession No. These sequences are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825.

Sequence identifiers are missing from claims 24-26. To avoid introduction of new matter the sequences submitted should be the sequences as they existed in GenBank at the time of filing.

Full compliance with the sequence rules is required in response to this Office action. A complete response to this Office action must include both compliance with the sequence rules and a response to the issues set forth below. Failure to fully comply with both of these requirements in the time period set forth in this Office action will be held to be non-responsive.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

4. Claims 2-8, 10-15 and 17-22 are objected to because of the following informalities:

Claims 2-8 should have a comma after "1".

Claims 10-15 should have a comma after "9".

Claims 17-22 should have a comma after "16".

The comma after "Vitamin C" in claim 6, line 2, and claim 13, line 2, should be deleted.

A comma should be inserted after "acid" in claim 7, line 3, claim 14, line 3, and claim 21, line 3.

The comma after "capacity" in claim 20, line 2, should be deleted.

Claim Rejections - 35 USC § 112

5. Claims 1-22 and 24-26 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection is modified from the rejection set forth in the Office action mailed 8 January 2002. Applicant's arguments filed 4 June 2002 have been fully considered but they are not persuasive.

The claims are broadly drawn to a method of increasing the endogenous level of vitamin C in a plant and increasing the resistance to environmental stress by expression a nucleic acid that encodes an enzyme in a plant biosynthetic pathway, wherein the enzyme is phosphoglucose isomerase, phosphomannomutase, GDP-mannose pyrophosphorylase (GMPase), or GDP-D-mannose-3,5-epimerase, and plants thereby obtained.

The instant specification only provides guidance for EMS mutagenesis of *Arabidopsis* to produce two mutants, named *vtc*, that are deficient in AsA production (pg 7-9); testing the mutants for loss of conversion from mannose to ascorbic acid (pg 9-10); AFLP mapping of the *vtc* loci - *vtc1* maps within a published BAC that has as one of its open reading frames a putative mannose-1-phosphate guanyltransferase, aka GDP-mannose pyrophosphorylase, and for which a partial sequence has been published in GenBank as Accession No. T46645; this sequence is mutated in *vtc1-1* and *vtc1-2* (pg 10-12); measuring GDP-mannose pyrophosphorylase activity in

vtc1 mutants (pg 12-13); and complementation of the *vtc1-1* mutant with a 3.4 kb subfragment from the BAC clone that has the GDP-mannose pyrophosphorylase gene (pg 13-17).

The instant specification fails to provide guidance for the sequence of the full-length gene encoding GMPase, for wild-type plants transformed with the GMPase gene, or for methods of making stress resistant plants by transformation with a nucleic acid encoding the GMPase gene.

Expression of a gene in plants is unpredictable. Sweetlove et al (1996, Biochem. J. 320:493-498) found no differences in starch content, tuber number, tuber weight, or metabolite content between potatoes transformed with a gene encoding ADP-glucose pyrophosphorylase and potatoes from control plants, even though the activity of the enzyme was four-fold higher in the transformed plants (pg 495, entire pg, and pg 497, right column, paragraph 3). Thiele et al (1999, Plant Physiol. 120:73-81) teach that in potato plants transformed with the *Arabidopsis* phytochrome B gene, the endogenous phytochrome B transcript levels were not significantly affected (pg 75, right column, paragraph 3, and Fig. 1). As the gene encoding the VTC4 gene product was not expressed plants, the unpredictability associated with expression of genes in plants has not been overcome.

Claim 22 is drawn to a method of increasing the level of Vitamin C in a plant wherein the method produces a plant that is edible. The specification fails to teach transformation of a plant with a gene in the vitamin C synthesis where the plant is converted from an inedible plant to an edible plant.

The claims are drawn to methods of increasing vitamin C levels in plants by transformation with any gene encoding GMPase, and plants so transformed. However, the only gene encoding GMPase taught in the instant specification is from Arabidopsis, and that is a fragment. The specification does not teach the sequence of a GMPase gene form any other plant.

The instant specification fails to provide guidance for the sequence of the full-length gene encoding GMPase. Thus, the invention appears to employ novel plasmid encoding GMPase contained in microorganisms. Since the plasmids contained in the microorganisms are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If the plasmids contained in the microorganisms are not so obtainable or available, the requirements of 35 USC 112 may be satisfied by a deposit of the microorganisms. The specification does not disclose a repeatable process to obtain the plasmids contained in the microorganisms and it is not apparent if the plasmids are readily available to the public. Thus, a deposit is required for enablement purpose.

If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;
(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;
(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the enforceable life of the patent, whichever is longer;
(d) a test of the viability of the biological material at the time of deposit (see 37 CFR 1.807); and,
(e) the deposit will be replaced if it should ever become inviable.

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate methods for increasing the endogenous level of vitamin C in a plant by overexpression by any

method of any enzyme crucial to vitamin C biosynthesis, including non-*Arabidopsis* GMPase, and plants thereby obtained.

Applicant urges that the claims are not drawn to expression or overexpression in wild-type plants but are directed to genetically engineered plants; thus, no enablement regarding overexpression of a gene in wild-type plants is required. Furthermore, Applicant argues that they have successfully expressed a gene encoding GMPase in plants, overcoming any unpredictability (appeal brief pg 7).

This is not found persuasive. Applicant on pg 16-17 transformed a mutant *vtc1-1* plant with the GMPase cDNA clone, effectively converting a mutant plant into a wild-type plant. This procedure is called complementation and the experiment merely showed that the cDNA was from the vtc1 gene. If the experiment had been unsuccessful, it would have shown the cDNA was not from the vtc1 gene.

Applicant did not transform a wild-type plant with the GMPase cDNA clone to show that the plants so produced have increased levels of vitamin C. Sweetlove et al (1996, Biochem. J. 320:493-498) and Thiele et al (1999, Plant Physiol. 120:73-81) teach that transformation of a gene into a wild-type plant is unpredictable and cannot be relied upon to increase the expression of the gene with which the plant was transformed. Note that increased expression and increased production of GMPase protein, relative to a wild-type plant, would be required for increased vitamin C synthesis.

Thus, Applicant has not overcome unpredictability of transformation with a gene encoding an enzyme in the vitamin C pathway.

Applicant is invited to submit a Declaration providing data showing that when the GMPase cDNA is transformed into wild-type plants, the resulting plants have increased levels of Vitamin C.

Applicant urges that genes encoding GMPase are will known in the art and thus are not required to be disclosed in the specification. Applicant urges that Figure 1 and the specification disclose the enzymes in the Vitamin C pathway and provides the sequence of the GMPase gene (appeal brief pg 7-9).

This is not found persuasive. Neither Applicant nor the prior art teach the sequence of full-length GMPase genes. GenBank Accession No. T46645 is only 510 nucleotides long and is only a portion of the full-length GMPase coding sequence. Figure 3 of the specification shows that the entire coding region is about 2.0 kb long, four times the length of GenBank Accession No. T46645. Transformation of a plant with a nucleic acid whose GMPase sequence consists only of the sequence in GenBank Accession No. T46645 would not even complement the vtc1-1 mutant. In order to practice Applicant's claimed invention, the full-length sequence is required. As this sequence is not taught in the art nor in the specification, a deposit of the GMPase cDNA is required for enablement.

Disclosure of a list of enzyme names does not provide enablement for the nucleic acids that encode such enzymes.

6. Claims 1-22 and 24-26 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is repeated for the reasons of record as set

forth in the Office action mailed 8 January 2002. Applicant's arguments filed 4 June 2002 have been fully considered but they are not persuasive.

Applicant urges that genes encoding GMPase and the other enzymes in the Vitamin C pathway are well-known in the art, and are not required to be disclosed in the specification. Applicant urges that Figure 1 and the specification disclose the enzymes in the Vitamin C pathway and provides the sequence of the GMPase gene (appeal brief pg 12-13).

This is not found persuasive. Neither Applicant nor the prior art describe the sequence of full-length GMPase genes. GenBank Accession No. T46645 is only 510 nucleotides long and is only a portion of the full-length GMPase coding sequence. Figure 3 of the specification shows that the entire coding region is about 2.0 kb long, four times the length of GenBank Accession No. T46645. The sequence of the rest of the GMPAse gene is not described in the specification.

Disclosure of a list of enzyme names does not describe the structural features, that is, the sequence, of the nucleic acids that encode such enzymes.

Applicant urges that the assertion of unpredictability with respect to overexpression is overcome by Applicant's expression of GMPase in a plant (appeal brief pg 12-14).

This is not found persuasive. This argument is not drawn to written description, but the enablement, and has been address above.

7. Claims 1-8, 10, 16-22 and 24-26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections.

Claim 1 is indefinite in its recitation of "plant Vitamin C biosynthesis pathway." It is not clear if this means the nucleic acid is derived from plants or if the nucleic acid encodes any pathway enzyme that can function in plants.

Claims 2 and 10 are indefinite in their recitation of "said plant, or portion thereof, is a dicot" Is Applicant saying that only a portion of the plant is a dicot? What is the rest of the plant? It is suggested that ", or portion thereof," be deleted.

The term "increasing" in claim 16 is a relative term that renders the claim indefinite. The term "increasing" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is suggested that the level of vitamin C be compared to that of a nontransformed plant.

Claim 20 lacks antecedent basis for the limitation "said genetically engineered plant" in lines 2-3.

Conclusion

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at (703) 308-0198.

Anne R. Kubelik, Ph.D.
June 12, 2003